

Impact of patient's clinical features on the recurring lung metastases of breast cancer

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Abstract

Aim: The aim of this study was to investigate the clinical features affecting on the recurrence of lung metastases of breast cancer.

Materials and Methods: Data of 92 patients who had undergone pulmonary metastasectomy of breast cancer were examined in terms of recurrence, age, type of primary breast cancer, disease free interval (DFI), PET/CT findings, side of metastasectomy and number of resected lung metastases.

Results: Solitary and unilateral pulmonary metastases presenting lower SUV following longer period of DFI were less involved in recurrence whereas invasive lobular and inflammatory carcinomas were more inclined to develop relapsing lung metastases. Age was not a risk factor for recurrence.

Conclusion: Identifying high risk patients for recurrence contributes to prevention of repeating and excessive surgeries.

Keywords: Breast cancer; clinical features; lung metastases; recurrence

INTRODUCTION

Breast cancer is the leading cause of malignancy related deaths in women as a consequence of its intrinsic predisposition to develop metastases even at the time of diagnosis or early stages (1-4).

Following the precise staging, surgical resection is the first of choice of treatment in non-metastasizing breast cancers where chemotherapy, hormonal therapy or radiotherapy are administered in pursuit of local invasion or distant organ dissemination (5,6).

Pulmonary resection complying with the approved criteria for lung metastasectomy contributes to prolonged survival. Regarding that lungs are common metastatic targets of breast cancer and recurrent pulmonary metastases are mostly eventual, identification of the patients who are more susceptible to develop recurrence provides benefit in choosing convenient cases for lung surgery and also composing an efficient treatment protocol.

The current literature consists of numerous studies, reviews and meta-analysis about long term survival of particular malignancies. This study dedicatedly aimed to evaluate the risk factors associated with the recurrence of lung metastases from breast cancer by focussing on the clinical features of the patients rather than the surgical outcomes.

MATERIALS and METHODS

A retrospective study was conducted to investigate 92 patients who had undergone pulmonary metastasectomy of breast cancer between 2005 and 2019. Patients who had lung metastases confirmed by pathological reports were included in the study whereas the exclusion criteria were uncomplete lung metastasectomy and inability to access the required patient data.

Ethical Considerations

This study was approved by Faculty's Ethics Committee (reference number: GOEK/42-67) and all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Procedures

All the patients were assessed with a respiratory function test and a contrast enhanced computed tomography on the last day before surgery. Main criteria for lung resection were completely resectable pulmonary metastases, adequate respiratory reserve and absence of residuary or recurrent tumor of primary breast cancer and also any extrapulmonary metastases. Lung resections were performed via lateral thoracotomy and three-port thoracoscopy by same team of surgeons which prevented the variations of surgical techniques and experience. For bilateral resections, a month of waiting time was scheduled between the interventions.

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Whole group of patients were evaluated in terms of age, type of primary breast cancer, side of operation, maximum standardized FDG uptake value (SUV) identified by F-18 fluorodeoxyglucose positron emission computed tomography (PET/CT) scan, disease free interval and the number of resected lung metastases. Types of primary tumor were listed as invasive ductal, invasive lobular, triple negative and inflammatory carcinoma. Side of the resection was recorded as unilateral or bilateral. In the presence of more than one lung metastases, SUV was accepted as the highest count among all the reported values. Disease free interval was noted as the time between the diagnosis of breast cancer and the pulmonary metastasectomy. Number of lung metastases was recorded as solitary, between 2 and 4 and counting for 5 or more. For bilateral resections, total number of resected metastases were calculated considering both sides.

Statistical Analysis

SPSS (IBM SPSS for Windows, ver.24) statistical package program was used for calculations. Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, minimum and maximum; categorical variables were expressed as number (n) and percentage (%). Independent samples t test was used to compare the averages of measurements and Chi-square test was employed to reveal the relation between categorical variables. The statistical significance level (α) was taken as 5%.

RESULTS

Mean age of the group who were all female was 54.4 ± 11.6 years. The majority of primary breast cancer was invasive ductal carcinoma diagnosed in 64 (69.6%) patients. Pulmonary metastases presented unilateral and bilateral localizations in 64 (69.6%) and 28 (30.4%) patients, respectively. Fifty one (55.4%) patients developed solitary lung metastases while the number of metastatic lesions

was between 2 and 4 for 32 (34.8%) and 5 or more for 9 (9.8%) patients. Mean SUV of lung metastases was 4.53 ± 1.83 whereas mean DFI was 41.1 ± 17.9 months for the whole group. Thirty two (34.8%) encountered recurrence in the lungs following the initial pulmonary metastasectomy. Related data were summarized in Table 1.

Table 1. Clinical features of the study group

| Continuous variables | Mean \pm Standard deviation | Minimum - Maximum |
|--------------------------------------|-------------------------------|-------------------|
| Age years | 54.4 \pm 11.6 | 29-79 |
| SUV | 4.53 \pm 1.83 | 1.2-11.3 |
| DFI months | 41.1 \pm 17.9 | 10-82 |
| Categorical variables | N | % |
| Number of lung metastases | | |
| Solitary | 51 | 55.4 |
| 2-4 | 32 | 34.8 |
| ≥ 5 | 9 | 9.8 |
| Type of primary breast cancer | | |
| Invasive ductal | 64 | 69.6 |
| Invasive lobular | 12 | 13 |
| Triple negative | 9 | 9.8 |
| Inflammatory | 7 | 7.6 |
| Side of lung metastasectomy | | |
| Unilateral | 64 | 69.6 |
| Bilateral | 28 | 30.4 |
| Recurrence of lung metastases | | |
| Yes | 32 | 34.8 |
| No | 60 | 65.2 |

SUV: FDG Uptake Value by PET/CT; DFI: Disease Free Interval

Comparison of the patients relating recurrence revealed no significant difference in terms of age ($P=0.06$). Invasive lobular and inflammatory types of breast cancer presented

Table 2. Factors related with the recurrent lung metastases of breast cancer

| Continuous variables | Recurrence of metastases | | P value |
|--------------------------------------|----------------------------|--------------------------|---------|
| | Yes | No | |
| Age years, mean \pm SD (min-max) | 51.3 \pm 12.2 (33-78) | 56.1 \pm 11 (29-79) | 0.060 |
| SUV mean \pm SD (min-max) | 6.11 \pm 1.79 (2.6-11.3) | 3.69 \pm 1.2 (1.2-6.7) | <0.001 |
| DFI months, mean \pm SD (min-max) | 21.8 \pm 5.87 (10-36) | 51.4 \pm 13 (20-82) | <0.001 |
| Categorical variables | Recurrence of metastases | | P value |
| | Yes | No | |
| Number of lung metastases | | | |
| Solitary | 6 | 45 | <0.001 |
| 2-4 | 17 | 15 | |
| ≥ 5 | 9 | 0 | |
| Type of primary breast cancer | | | |
| Invasive ductal | 16 | 48 | 0.007 |
| Invasive lobular | 8 | 4 | |
| Triple negative | 3 | 6 | |
| Inflammatory | 5 | 2 | |
| Side of lung metastases | | | |
| Unilateral | 5 | 59 | <0.001 |
| Bilateral | 27 | 1 | |

SD: Standard Deviation; Min: Minimum; Max: Maximum; SUV: FDG Uptake value by PET/CT; DFI: Disease Free Interval

predisposition to develop recurrent lung metastases ($P=0.007$). Moreover, higher SUV values and shorter DFI were closely associated with a relapse ($P<0.001$). The patients who had initially developed solitary metastases in the lung experienced the risk of recurrence at least whereas increasing number of metastatic pulmonary lesions was correlated with a potential recurrence ($P<0.001$). Likewise, the preliminary presentation of metastases in both lungs was significantly affined with the development of relapse ($P<0.001$). Comparison of study variables was defined in Table 2.

Among 32 patients who had developed recurrence, 12 (37.5%) underwent pulmonary metastasectomy once again while rest of the cases were admitted to oncological treatment due to disseminated disease in the lung or distant metastases.

DISCUSSION

The findings of this study clearly show that clinical features of the patients with breast cancer constitute differential effects on the development of lung metastases.

Breast cancer is presented with metastases at the time of primary diagnosis at a rate up to 10% (6,7). Over half of the patients with advanced breast cancer encounter lung metastases hence the most common metastatic targets are lungs, bones and liver (7-9). Pulmonary metastases when accompanied by malignant pleural effusion do not only deteriorate the quality of life but also reduce the median survival time to 15 months (10).

Regardless of the primary tumor type, complete resection of lung metastases provides 5-year survival up to 50% with a median survival of 35 months while median survival is 10-20 months and the 5-year survival ranges between 10% and 25% following systemic therapies (11-13). In consideration of this conclusion, surgery has been accepted as the first choice of curative treatment for totally resectable metastasis and tireless effort to expose prognostic factors following an accomplished metastasectomy persists.

Good prognostic factors for lung metastases of breast cancer were reported as complete resection of pulmonary lesions, $DFI \geq 36$ months, solitary and unilateral lung metastases (14-16). However, feasibility of implementing these criteria to reveal the risks for the development of recurrence is controversial due to limited number of recent studies. The findings of this study confirm that solitary and unilateral lung metastases of breast cancer are inclined to relapse to a lesser extent and period of 36 months forestated for DFI as the threshold value of recurrence risk is prevailing.

Recent studies frequently reported that ages under 40 and over 80 years were independent prognostic factors for poor survival of breast cancer (13-15). However, data correlating age with the recurrence of breast cancer particularly metastatizing to lungs do not exist in the literature. Similarly, this study failed to identify age as a risk factor for the development of recurrence.

PET/CT was advocated to be more accurate than conventional imaging in the detection of lymph node and metastases of breast cancer and also well correlated with absence of metastatic disease when negative FDG uptake was present (17-19). However, many recent studies reported different FDG avidities of primary tumor and metastases suggesting that traditional systemic evaluation and follow-up protocols of breast cancer were still valid (20-23).

Studies in the current literature frequently announced advanced stage and negative hormone receptor status as independent prognostic factors for poor survival rates but failed to reveal a correlation between the pathological type of primary breast cancer and long-term survival (24,25). Likewise, the impact of breast cancer type over the recurrence of distant metastases remains unclear.

In this series, the two unprecedented issues were significantly involved in the recurrent lung metastases of breast cancer. First, detected mean SUV was almost twice as much for the recurrence developing group of patients. Broadly, lung metastases presenting a SUV value over 6 may arouse suspicion of a potential relapse. Second, type of primary breast tumor apparently affiliated with the expectation of a recurrence. Patients with invasive lobular and inflammatory breast cancers were more susceptible to experience a relapse even after well accomplished lung metastasectomies.

Regarding that 37.5% of the cases who had encountered recurrence of lung metastases were applicable for a repeating metastasectomy, this study underlines the importance of clinical features of the patients to predict potential relapses by identifying high risk patients.

There has been limited data related with indications of pulmonary metastasectomy for breast cancer concerning that very good survival rates can be achieved with non-surgical treatments even in advanced cases (4-7). Patients with confirmed lung metastases should be attentively selected for surgery upon the consensus of oncologist, pulmonologist and thoracic surgeon to prevent redundant lung resections which may result as potential mortality and morbidity.

LIMITATIONS

The principal limitations of this study were the design as a single center workup and lack of data comparison due to absence of similar studies in the literature.

CONCLUSION

Predicting the recurrence of a metastatic malignancy contributes to prevent extended surgical interventions and inappropriate treatment protocols. Moreover, identifying the patients with escalated risk of recurrence is beneficial for the surgeons prior to the final decision of sequential pulmonary metastasectomies.

Competing interests: The authors declare that they have no competing interest.

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